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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/060,521	01/30/2002	John P. Mueller	PC11013A	8456

28523 7590 07/15/2005

PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
EASTERN POINT ROAD
GROTON, CT 06340

EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/060,521	MUELLER ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *1 and 4-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/25/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence alignment*.

DETAILED ACTION

Petition Decision

1) It is noted that the decision issued 10/25/04 on Applicants' petition filed 04/29/04 states that a *new* Office Action be mailed out.

Election

2) Acknowledgment is made of Applicants' election filed 05/27/03 in response to the restriction requirement mailed 04/10/03. Applicants have elected invention III, claims 2 and 3, with traverse. Applicants' traversal is on the grounds that a search for all of the claims in the application would not be an undue burden on the Office, because all of the claims are drawn to *harA* genes or proteins and methods of using them. Applicants acknowledge that methods of screening for the ability of a compound to bind a target are *different* from the methods of screening for the ability of a compound to inhibit a target, but argue that the searches for the two methods will be 'almost completely identical'. Applicants submit that searching for the sequence of the gene *and* protein as well as searching for the name thereof will 'likely' comprise the bulk of the search.

Applicants' arguments have been carefully considered, but are non-persuasive. As set forth in the restriction requirement mailed 04/10/03, the methods of inventions I and II differ from the methods of inventions III and IV and the methods of V-VIII in method steps and parameters, compositions or reagents used, and the ultimate goals accomplished. Furthermore, a compound that binds a polypeptide need not and does not necessarily inhibit the activity of the polypeptide. Inventions IX through XIV are directed to distinct products, which differ form one another materially, structurally, and functionally or biologically. Although the amino acid sequences of SEQ ID NO: 2 and 4 as well as the nucleotide sequences of SEQ ID NO: 1 and SEQ ID NO: 3 belong to the same classes and subclasses respectively, these products differ from one another in their structure or composition, thus requiring separate and non-coextensive searches. The nucleotide sequences belong to class 536, whereas polypeptides belong to class 530; and the methods belong to class 435. The two bacterial products of inventions XI and XII differ from one another antigenically and genus- and species-wise, and require separate searches because of their structural distinctness. For these reasons, the restriction set forth in the instant application is deemed proper and is hereby made FINAL.

Status of Claims

3) Claims 1-17 are pending.

Claims 1 and 4-17 have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 2 and 3 are under examination. A First Action on the Merits for these claims is issued

Information Disclosure Statement

4) Acknowledgment is made Applicants' Information Disclosure Statement filed 03/25/04. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Sequence Listing

5) Acknowledgment is made of Applicants' submission of the raw sequence listing and the CRF, which have been entered.

Priority

6) The Oath/Declaration filed in the instant application claims priority to the provisional application, 60/265,034, filed 01/30/01.

Drawings

7) Acknowledgment is made of Applicants' submission of the drawings filed 01/30/02.

Specification - Informalities

8) The specification is objected to for the following reasons:

(a) The first paragraph of the specification does not provide the priority information as indicated above under 'Priority'.

(b) The instant specification is objected to because it contains embedded hyperlinks and/or other forms of browser-executable code, which Applicants are required to delete. For example, see lines 16 and 19 on page 2; line 11 on page 29; and lines 23 and 28 on page 23 of the specification. See MPEP § 608.01.

(c) The 'Brief Description of the Drawings' on page 27 of the specification is objected to. While the actual drawings identify the Figures as Figures 1A and 1B; Figures 2A and 2B;

Figures 3 A and 3B; and Figures 4A and 4B, under the 'Brief Description of the Drawings' on page 27 of the specification does not refer to the four figures as Figures 1A and 1B; Figures 2A and 2B; Figures 3 A and 3B; and Figures 4A and 4B respectively. Amendments to page 27 of the specification are suggested to reflect this. References to these Figures throughout the specification should be amended accordingly.

(d) The use of the trademarks in the instant specification has been noted in this application. For example, see pages 47 and 48: 'Ficoll'. Although the use of trademarks is permissible in patent applications, the propriety nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification and make necessary changes wherever trademark recitations appear.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

9) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

10) Claims 2 and 3 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 2 is vague and indefinite in the abbreviated recitation 'harA'activity, because it is unclear what does this activity represent. It is suggested that the abbreviation be recited as a full terminology at first occurrence in the independent claim, with its abbreviated recitation retained in parentheses.

(b) Claim 3 is vague and indefinite in the abbreviated recitation, for example, 'NTPase', because it is unclear what does this stand for. It is suggested that the abbreviation be recited as a full terminology at first occurrence, with its abbreviated recitation retained in parentheses.

(c) Claim 2 is indefinite in the recitation 'shown in Figure 2', because it is unclear what is included or excluded by the claim language. According to M.P.E.P 2173.05(s), where possible, claims are to be complete in themselves. Incorporation by reference to Tables or Examples and Figures, as in this case, is a necessity doctrine, not for Applicants' convenience. See *Ex parte*

Fressola, 27 USPQ2d 1608, *1609 (Bd. Pat. App. & Inter. 1993)*. Figure 2 is also subject to changes via amendments. Such amendments to Figure 2 would change the scope of the claim. To obviate the rejection, it is suggested that Applicants recite the SEQ ID number without referring to any Figure, since such a reference is unnecessary.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

11) Claims 2 and 3 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

It is noted that the harA polypeptide recited in the claimed method does not exist independent of its function, i.e., harA or NTPase activity. The specification discloses diagnostic applications or screening intentions for the harA polypeptide. However, the instant specification fails to teach a single variant of a polypeptide sequence having 75% identity to the amino acid sequence of SEQ ID NO: 2 and concurrently having the harA or NTPase activity. Diagnostic or screening applications minimally require a specific interaction with a compound. The precise structure or relevant identifying characteristics of DNA molecule that encode a variants harA polypeptide having 75% identity to the amino acid sequence of SEQ ID NO: 2 and the harA or NTPase functional activity can only be determined empirically by actually making DNA molecules that encode the polypeptides of the recited variability, i.e., the instantly recited 75% sequence identity, and testing he varied DNA molecules to determine whether they encode the 75% modified polypeptide variants having the particularly disclosed harA or NTPase activity. The *Written Description Guidelines* state:

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between the structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function.

A mere statement that the invention or the method includes the use of a polypeptide having 75% identity to the amino acid sequence of SEQ ID NO: 2 is insufficient to meet the adequate written description requirement of the claimed invention. The polypeptide of SEQ ID NO: 2 has specific biologic properties dictated by the structure of the polypeptide and the corresponding structure of

the structural gene sequence which encodes it. A convincing structure-function relationship has to exist between the structure of the gene sequence, the structure of the polypeptide encoded, and the function of the encoded polypeptide. The function cannot be predicted from the modification of the structure of the gene and in the instant case, the DNA encoding the at least 75% modified polypeptide variant. Applicants have not shown that variation or modification of a reference sequence encoding a reference polypeptide as claimed would automatically predict the production of a polypeptide having the recited functional activity, i.e., harA activity. The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of DNA molecules encoding a representative number of species of polypeptide variants of at least 75% sequence identity as recited, sufficient to allow one skilled in the art to determine that the inventors had possession of the invention as claimed. With the exception of a polypeptide of SEQ ID NO: 2, a skilled artisan cannot envision the detailed chemical structure of all the polypeptide variant species encompassed by the recited molecule. Regardless of the complexity or simplicity of the method of isolation, conception cannot be achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that its is a part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)* and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.*

12) Claims 2 and 3 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of screening a compound to determine whether the compound inhibits NTPase activity of a harA polypeptide by measuring the NTPase activity of the polypeptide having the amino acid sequence of SEQ ID NO: 2, in the absence and in the presence of the compound as recited, does not reasonably provide enablement for a method of screening a compound to determine whether the compound inhibits NTPase activity by measuring the activity of a harA polypeptide comprising an amino acid sequence at least 75% identical, i.e., less that 100% identical, to SEQ ID NO: 2 as claimed broadly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue

experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

Instant claims are drawn to a screening method to determine whether a compound inhibits the generic harA activity or the specific NTPase activity of a harA polypeptide having at least 75% identity to the amino acid sequence of SEQ ID NO: 2, in the presence and absence of the compound. The method requires contacting the polypeptide variant having such a function or activity with an inhibitory compound. The claimed method *requires* that the harA polypeptide that comprises an amino acid sequence at least 75% identical to SEQ ID NO: 2 possess harA or NTPase activity so that a decrease in the activity can be measured in the presence of a compound by comparing to the activity in the absence of the compound. In other words, the recited polypeptide variant having at least 25% dissimilarity with the amino acid sequence of SEQ ID NO: 2 is *required* to have the harA or NTPase activity such that the ability of a compound to inhibit the harA or NTPase activity can be measured by the claimed screening method. However, the instant specification does not teach how to make a polypeptide of the amino acid sequence SEQ ID NO: 2 with 25% of its amino acids varied or modified in such a way that the resultant polypeptide variant still maintains the harA or NTPase activity. Neither the specification nor the art discloses a polypeptide variant that is at least 25% non-identical to the amino acid sequence of SEQ ID NO: 2 which variant retains the harA or NTPase activity. The instant specification fails to demonstrate that a polypeptide variant having at least 75% identity to SEQ ID NO: 2, if prepared by one of skill in the art, would retain all the functional or biological properties of the native harA polypeptide of SEQ ID NO: 2. It should be noted that predictability or unpredictability is one of the *Wands* factors for enablement. The precise structural composition of the claimed polypeptide variant is not disclosed, without which one of ordinary skill in the art cannot make and use the claimed product in the claimed method without undue experimentation. The specification lacks disclosure as to how to

produce a polypeptide variant having at least 75% sequence identity to SEQ ID NO: 2 and at the same time having all the necessary functions for use as a screening assay reagent. There is no evidence within the instant specification showing that the claimed polypeptide variant having an amino acid sequence which is 'at least 75%' identity to the amino acid sequence of the polypeptide of SEQ ID NO: 2, does in fact have the recited harA or NTPase activity. There is no predictability that such a polypeptide variant having as much as 25% dissimilarity with the polypeptide of SEQ ID NO: 2, would remain functional as an effective reagent in a screening assay method. This is critical because the art reflects sensitivity of proteins or polypeptides to alteration of even a single amino acid residue in its amino acid sequence. An alteration in a single amino acid can eliminate or drastically change one or more function(s) of the polypeptide. For instance, Burgess *et al* (*J. Cell Biol.* 111: 2129-2138, 1990) taught that replacement of a single lysine residue at position 118 of the protein, acidic fibroblast growth factor, by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Lazar *et al* (*Mol. Cellular Biol.* 8: 1247-1252, 1988) provided similar teachings and showed that in the protein, transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity, while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. In the instant case, it is unlikely that a polypeptide molecule having as much as 25% dissimilarity with the native polypeptide of SEQ ID NO: 2 as recited, would have its primary, secondary or tertiary structure unchanged and would have the harA or NTPase activity retained. The effects of such a high dissimilarity upon the polypeptide structure and function are unpredictable. One of skill in the art cannot predict that such a polypeptide variant would have its immunologic or biologic specificity retained. Bowie *et al.* (*Science* 247: 1306-1310, 1990) taught that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie *et al.* further taught that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (see column 1 on page 1306). Bowie *et al* also taught that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function(s) is limited.

Certain positions in the polypeptide sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (see column 2 on page 1306). Thus, while the art demonstrates that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein or polypeptide, with as much as 25% dissimilarity to the polypeptide of SEQ ID NO: 2, the harA or NTPase activity of the claimed polypeptide variant could not be predicted, based solely on the sequence identity, nor would it be expected to be the same as that of the polypeptide of SEQ ID NO: 2. For example, if one nucleotide in the nucleotide sequence that encodes the polypeptide of SEQ ID NO: 2 is deleted or inserted at a single position within the coding sequence, all the codons down stream of that insertion or deletion would be frame-shifted. If that frame-shift took place near the 5' end of the gene, it is likely that the polypeptide expressed will have little in common structurally or functionally with the native polypeptide of SEQ ID NO: 2. There is no certainty that amino acid substitutions at any position would yield a harA polypeptide that retains the function and/or the specificity of the native harA polypeptide. The specification fails to demonstrate that a polypeptide having 25% structural dissimilarity to SEQ ID NO: 2 would be functionally equivalent to the native polypeptide of SEQ ID NO: 2 particularly with regard to the harA or NTPase activity and hygromycin resistance. One simply cannot predict what effects a given deletion, insertion or modification in the amino acid sequence would cause, and therefore such modified molecules are not enabled as Applicants' invention. Applicants have not enabled the full scope of the invention as claimed for those polypeptide molecules which are altered or varied. The specification only discloses a harA polypeptide of SEQ ID NO: 2. Undisclosed and unidentified functional polypeptide molecules of at least 25% identity encompassed in the claims are not enabled for their scope. Although a skilled artisan might envision making a number of changes in the reference polynucleotide sequence in accordance with Applicants' disclosure, it is highly uncertain that the polypeptide variant as recited would be functionally equivalent to the native harA polypeptide of SEQ ID NO: 2. The altered polypeptide would vary in an unknown or unpredictable manner from the disclosed native polypeptide sequence. For these reasons, making and using of the instantly claimed polypeptide variant having the desired function(s) is well outside the realm of routine experimentation. Accordingly, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to

reproducibly practice the invention as claimed due to the lack of specific guidance, the lack of enabling disclosure, the art-demonstrated functional unpredictability as recognized in the state of the art, and the quantity of experimentation necessary. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C § 102

13) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language.

14) Claim 2 is rejected under 35 U.S.C § 102(e)(1) as being anticipated by Davis *et al.* (WO 01/79257).

It is noted that one of the activities of the harA polypeptide is mediation of drug resistance.

Davis *et al.* disclosed a screening method for determining whether a test substance reduces efflux of antibacterial agents from a cell, the method comprising contacting MDR efflux pump Abc11, i.e., a polypeptide having SEQ ID NO: 22 produced by a non-bacterial cell with the test substance; contacting the cell with a compound that is capable of entering the cell and being transported by the MDR efflux pump; and measuring efflux of the compound from the cell, wherein decreased efflux, relative to a cell not contacted with the test substance, identifies the test substance as containing a compound that reduces efflux of antibacterial agents from a cell. See claims 27 and 18. Davis *et al.* disclosed a screening method for determining whether a test substance or a compound blocks (i.e., inhibits) efflux of an antibacterial agent from a cell comprising contacting the polypeptide, Abc11 (SEQ ID NO: 22), with the test substance and determining whether the compound or the test substance binds to the polypeptide, wherein binding of the compound or the test substance identified it as a compound that blocks efflux of an antibacterial agent from a cell (see claim 13). The method is performed in a cell or in a cell-free system (see paragraph bridging pages 7 and 8). Davis *et al.* disclosed a method for determining whether a test substance reduces

efflux of antibacterial agents from a cell by contacting an enterococcal MDR efflux pump, Abc11 polypeptide having SEQ ID NO: 22, with the test substance and measuring the efflux , wherein decreased efflux relative to a cell not contacted with the test substance identifies the test substance as containing a compound that reduces efflux of antibacterial agents from a cell (see paragraph bridging pages 11 and 12; claims 27 and 18; and Figure 25). The prior art Abc11 polypeptide having SEQ ID NO: 22, which shows 99.3% structural or sequence identity with the instantly recited SEQ ID NO: 2, functions as a multiple drug resistance (MDR) efflux pump and confers resistance to a variety of chemically unrelated agents (see page 1 and Figure 25). See the attached sequence alignment. The ability of the test substance to inhibit the polypeptide activity is determined by comparing its activity in the presence and in the absence of the test substance (see page 15). The method includes the steps of contacting the MDR efflux pump, i.e., the polypeptide, expressed by a cell with the test substance and measuring the expression of the MDR efflux pump. Decreased polypeptide expression relative to a cell not contacted with the test substance indicates that the test substance decreases expression of an MDR efflux pump. Decreased efflux in the presence of the test substance identifies the test substance as a compound that blocks efflux through the MDR efflux pump (see page 37). The prior art polypeptide having as high as 99.3% structural identity with the instantly recited SEQ ID NO: 2 is viewed as inherently having the harA activity.

Claim 2 is anticipated by Davis *et al.*

Objection(s)

15) Claim 2 is objected to for including non-elected subject matter.

Remarks

16) Claims 2 and 3 stand rejected.

17) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The central Fax number for submission of amendments, responses and papers is (703) 872-9306.

18) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may

be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

July, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER

SEQ ID NO. 2

```
RESULT 2
ABB47285
ID   ABB47285 standard; Protein; 498 AA.
XX
AC   ABB47285;
XX
DT   31-JAN-2002  (first entry)
XX
DE   Enterococcus faecalis polypeptide Abc23.
XX
KW   MDR; efflux pump; multidrug resistance; antibacterial; drug target.
XX
OS   Enterococcus faecalis.
XX
PN   WO200179257-A2.
XX
PD   25-OCT-2001.

     12-APR-2001; 2001WO-US12230.

PR   14-APR-2000; 2000US-197349P.
XX
PA   (PHYT-) PHYTERA INC.
XX
PI   Davis DV,  Rogers BL,  White AC;
XX
DR   WPI; 2001-626526/72.
DR   N-PSDB; ABA82960.
XX
PT   Determining whether a candidate nucleotide or polypeptide
PT   encodes/functions as a multidrug resistance (MDR) efflux pump comprises
PT   searching a database of nucleotide/polypeptide sequences for those with
PT   high identity to known MDR pumps -
XX
PS   Claim 10; Fig 26; 139pp; English.
XX
CC   The invention relates to determining whether a candidate nucleotide
CC   (ABA82938-ABA82971) or polypeptide (ABB47263-ABB47296) encodes/functions
CC   as a multidrug resistance (MDR) efflux pump comprising, searching a
CC   database for sequences high identity known MDR efflux pumps and then
CC   deleting/mutating an identified region of the DNA in a bacterial cell and
CC   determining whether the bacterial cell exhibits increased or decreased
CC   sensitivity to an antibacterial agent The identified pumps are useful for
CC   further identifying MDR efflux pumps that may be used as drug targets to
CC   increase the sensitivity of cells to antibacterial agents. Cells
CC   comprising the identified pumps may be used to screen for potential
CC   blockers or inhibitors of MDR pump function or gene expression.
XX
SQ.  Sequence   498 AA;

  Query Match             99.3%;  Score 2522;  DB 22;  Length 498;
  Best Local Similarity   99.2%;  Pred. No. 5.5e-189;
  Matches  494;  Conservative    2;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          1 MSKIELKQLSPAYDNQEVLLPDQANITMDTNWKLGLIGRNGRGKTTLLRLLQKQLDYQGE 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MSKIELKQLSPAYDNQEALLPDQANITMDTNWKLGLIGRNGRGKTTLLRLLQKQLDYQGE 60

Qy         61 ILHQVDFVYFPQTVAEEQQLTYYVLQEVTSFEQWELERRLTLLNVDPEVLWRPFSSLSGG 120
              ||||||||||||||||||||||||||||||||||:||||||||||||||||||||||||
Db         61 ILHQVDFVYFPQTVAEEQQLTYYVLQEVTSFEQWKLERRLTLLNVDPEVLWRPFSSLSGG 120

Qy        121 EKTKVLLGLLFIEENAPFLIDEPTNHLDLAGRQQVAEYLKKKKHGFILVSHDRAFVDEVV 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 EKTKVLLGLLFIEENAPFLIDEPTNHLDLAGRQQVAEYLKKKKHGFILVSHDRAFVDEVV 180

Qy        181 DHILAIEKSQLTLYQGNFSIYEEQKKLRDAFELAENEKIKKEVNRLKETARKKAEWSMNR 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 DHILAIEKSQLTLYQGNFSIYEEQKKLRDAFELAENEKIKKEVNRLKETARKKAEWSMNR 240

Qy        241 EGDKYGNAKEKGSGAIFDTGAIGARAARVMKRSKHIQQRAETQLAEKEKLLKDLEYIDPL 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 EGDKYGNAKEKGSGAIFDTGAIGARAARVMKRSKHIQQRAETQLAEKEKLLKDLEYIDSL 300

Qy        301 SMDYQPTHHKTLLTVEELRLGYEKNWLFAPLSFSINAGERVGITGKNGSGKSSLIQYLLD 360
              ||||||||||||||||||||||||||||||:||||||||||||||||||||||||||||
Db        301 SMDYQPTHHKTLLTVEELRLGYEKNWLFAPISPSINAGERVGITGKNGSGKSSLIQYLLD 360

Qy        361 NPSGDSEGEATLAHQLTISYVRQDYEDNQGTLSEFAEKNQLDYTQFLNNLRKLGMERAVF 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 NPSGDSEGEATLAHQLTISYVRQDYEDNQGTLSEFAEKNQLDYTQFLNNLRKLGMERAVF 420

Qy        421 TNRIEQMSMGQRKKVEVAKSLSQSAELYIWDEPLNYLDVFNHQQLEALILSVKPAMLVIE 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 TNRIEQMSMGQRKKVEVAKSLSQSAELYIWDEPLNYLDVFNHQQLEALILSVKPAMLVIE 480

Qy        481 HDAHFMKKITDKKIVLKS 498
              ||||||||||||||||||
Db        481 HDAHFMKKITDKKIVLKS 498


Search completed: July 28, 2003, 15:39:59
Job time : 99 secs
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